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Abstract

Conflict of interest in clinical research

Increased focus on ethical review of research demands a number of improvements in the existing system. Although these are being implemented, some factors that have received less attention in the past could be examined. One of these is conflict of interest. Such conflicts could exist for investigators, ethics committee (EC) members, and even the regulators. Guidance for identification and management of conflicts has been issued by many countries and Indian rules also speak about these conflicts. Greater clarity would help investigators and ECs manage conflicts more effectively. It is admitted that conflicts cannot be done away with, but their timely identification, disclosure, and management can reduce their impact and bring more transparency and accountability to trials in this country.

Key words: Competition, conflict, ethics, financial interest, loyalty

INTRODUCTION

A conflict of interest (COI) occurs when an individual who is involved in multiple interests has one interest that interferes with another. The terms ‘conflict of interests’ and ‘competing interests’ are used interchangeably. Another way of describing a COI is:

“A conflict of interest is a set of circumstances that creates a risk that professional judgement or actions regarding a primary interest will be unduly influenced by a secondary interest”.^[1]

A more comprehensive definition of COI preferred by the National Research Ethics Advisory Panel (NREAP) of United Kingdom (UK) is

“...a set of conditions in which professional judgment concerning a primary interest (such as patients’ welfare or the

validity of research) tends to be unduly influenced by a secondary interest (such as financial gain)”.^[2]

Some journals use the term ‘competing interest’, and the journal Nature defines competing interests as follows:

“...those of any kind that could undermine the objectivity, integrity or perceived value of a publication through their potential influence on behavior or content or from perception of such potential influence”.^[3]

Thus, a COI can be differentiated from a competing interest, in that the former affects research as a whole, whereas the latter affects the publication process.

A COI occurs in many professions but has serious impact in medical practice and medical research, as a patient’s life is often at stake. The mere presence of a COI does not imply an impropriety but suggests the risk of one, and if detected or declared in time, the impropriety can be prevented or at least its impact minimized.

In clinical research, the aim of therapeutic studies is to verify the safety and establish the efficacy of new drugs/devices. Though this is the primary aim of the study, the safety and well-being of the participants is more important than the eventual benefit of the drug to the society. As per the

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good clinical practice (GCP) guidelines of the International Conference on Harmonization (ICH), the health and medical care of the participants is the responsibility of the investigator, hence any COI of the investigator is a risk for the participant.

At a higher tier, the ethics committee (EC) provides oversight to the trial at the site and hence any COI affecting a member of the EC is a potential risk, though the level of risk could be lower than that of the investigator. Nonetheless, it is a risk and hence all efforts should be made to identify and eliminate it. For a fair and honest review by the EC, it is necessary to ascertain that no COI exists for the members approving and reviewing studies.

At a still higher level, the regulators have powers that go beyond those of the investigators and EC members; COI at that level will affect not only clinical research but also the eventual approval of drugs in the country. However, the regulator's COI is beyond the scope of this paper, and the author shall stop at expressing hope that the government ensures that there is no COI at the level of the regulators.

It should be remembered that a COI does not imply an impropriety but can lead to one. Given the present climate of suspicion that surrounds clinical research, investigators and EC members should be like Caesar's wife—above suspicion. No person with a COI should be allowed to take any decisions regarding the subjects or approval of trials.

INVESTIGATORS' COI

A COI arises mostly out of investigators' relation with the sponsor; senior physicians or surgeons are often advisers or members on the boards of pharmaceutical companies that sponsor clinical trials, leading to a COI. An obvious COI exists, if an investigator has certain relationships with a company or organization that could lead them to benefit financially or commercially from the outcome of a trial. There are other relationships that investigators have, that are intangible. They are implicit in the role of being a 'researcher' and could include a legitimate interest in completing a study.

Many universities and institutes in India have implemented a policy, requiring teachers and postgraduate students to publish at least two papers annually,^[4] though facilities for research may be sadly lacking. This could lead to a real need to publish, simply to retain their present position or to seek advancement in their positions. It is acknowledged that these are conflicts that are difficult to avoid, but by deft handling their impact could be minimized.

Although most COIs are in relation to sponsors, a contract research organization (CRO) is sometimes involved. Then,

the CRO takes the responsibility of the sponsors, thus COI could be due to relation with the CRO too. For the purpose of simplicity, the sponsor and CRO are treated as a single entity and labelled as 'sponsor'. Investigators with such relations are torn between their loyalty to the company and to the patient, hence the risk to the patient.

For a site or the EC, it is difficult to delve into the responsibilities that an investigator may hold outside the hospital; hence they depend on the investigator to declare such a relation. This raises an interesting problem that falls in the class of Murphy's laws. Any investigator, who has the honesty and integrity to declare such a COI, would probably not commit an impropriety due to the COI. Not all people allow their financial interests to interfere with their responsibilities to the society. However, an investigator who hides such a relation might not be honest enough to keep these interests separate.

What an investigator should declare is not laid down in any regulation, but the policy of the British Medical Journal advises investigators by saying the following:

"We are restricting ourselves to asking directly about competing financial interests, but you might want to disclose another sort of competing interest that would embarrass you if it became generally known after publication".^[5]

A more complicated situation arises when an investigator has invested in a company that is sponsoring the trials or could benefit due to the conduct of trials. Investments in companies could take two forms as shares or fixed deposits. Many investigators have a financial portfolio that includes shares of a number of companies, some of which are holding companies and own pharmaceutical companies.

There is, however, a serious error in this assumption, in that it equates all individuals. There is no evidence to suggest that all individuals are equally corruptible. In fact, some people might fall prey to the conflict at a low level, whereas another may not fall prey even at a high level. Nonetheless, there is a need to define a level above which all financial interests will have to be viewed with suspicion.

The Department of Health and Human Services (DHHS) of the United States (US) recognizes that some conflicting financial interests in research may affect the rights and welfare of human subjects. It suggests that institutional ECs and investigator both have the responsibility of identifying such conflicts and to ensure that these do not compromise the protection of human subjects.^[6]

The DHHS enjoins the institutional review boards to consider the following points:

1. What financial relationships could cause potential COI?
2. At what level should these conflicts be eliminated or managed?
3. What procedures will be helpful to
 - a. Collect and evaluate information regarding financial relations
 - b. Determine if they can cause a COI
 - c. Determine actions to protect participants
4. Who should be educated regarding COI
5. Who should examine individuals' financial relationships?
7. Expert testimony
8. Other remuneration (trips, gifts, in-kind payments, etc.)

In the US, the level above which a financial relationship is considered to be COI is 10,000 US dollars (USD) and in case of ownership of a company, at 5%.^[7] It should be remembered that COI is determined by the amount or percent ownership (whichever is lower). For a large company like Pfizer, 5% of the ownership means an investment in few billion dollars.

In the US, it was observed that over 90% physicians had a relationship with the pharmaceutical industry, most of them receiving food or samples of drugs.^[8] An American study has determined that around 25% of investigators had investments in sponsor companies beyond this amount.^[9] A study of 10 universities^[10] and that of 297 universities and institutes^[11] revealed that most had uniform policies for declaration of financial interests, but they varied considerably in their method of managing the COI.

In the UK, an investigation by the British Medical Journal revealed that more than 33% of general practitioners had a COI due to investment in pharmaceutical companies.^[12] To help investigators and administrators, the Oxford University has a set of procedures requiring disclosure of COI, including an annual declaration of significant financial interests. A significant financial interest is said to exist if the value of any remuneration received from the entity in the 12 months preceding the disclosure, and the value of any equity interest in the entity as of the date of disclosure, when aggregated, exceeds £ 5,000.^[13]

Cancer Research UK has listed eight types of relationships between investigators and sponsors that constitute a COI and these are as follows:

1. Employment, directorship, or leadership position
2. Advisory role (paid or unpaid)
3. Stock ownership or options
4. Any other direct or indirect financial interest (e.g., via rewards to inventors)
5. Honoraria-payments for specific speeches, seminar presentations, or appearances
6. Research funding

Cancer Research UK requires declaration of any of the above relationships of the investigators, their immediate family, spouses or partners, and children and limits remuneration (of all types) to less than £ 5000 per year, thus also requiring an annual declaration of COI.^[14] The NREAP of UK has a comprehensive policy on COI that suggests possible solutions for COI as well as guidance for declaration of COI.^[15]

The Indian GCP guidelines issued by the Central Drugs Standards and Control Organization (CDSCO), have adopted ethical guidelines (2000) of the Indian Council of Medical Research (ICMR). These guidelines mentions COI and state under the general principles (2.4.1.g) that

“...the research or experiment will be conducted in a fair, honest, impartial and transparent manner, after full disclosure is made by those associated with the Study of each aspect of their interest in the Study, and any conflict of interest that may exist”;^[16]

Whatever level of investment is decided upon to constitute a COI, it is sure to be challenged. It is admitted that there is little logic for choosing a particular level, nonetheless a line needs to be drawn somewhere, so that we may say that an investment below this level does not constitute a COI, whereas that above it, does. Like the US and UK, we need to define which family members' relation with an industry should be deemed to be a COI.

Elaborating on the issue of compensation, the Indian GCP guidelines speak of the need for *“...strong review to probe possible conflicts of interest between scientific responsibilities of researchers and business interests (e.g. ownership or part-ownership of a company developing a new product)”*

Organizations are required to develop methods to identify and manage COI, but as stated earlier, the Indian guidelines such as GCP and ICMR's revised ethical guidelines do not define a level of financial involvement that constitutes a COI. It is admitted that the CDSCO calls its GCP as guidelines. In the section of responsibilities of the sponsor in the Drugs and Cosmetics Rules (1945), it is specified that trials conducted in India must be performed in compliance with the GCP guidelines of CDSCO. The letter of approval from the Drugs Controller General of India (DCGI) also mentions this condition.

Among the commitments required to be given by an investigator are

“...I will ensure that the requirements relating to obtaining informed consent and ethics committee review and approval specified in the GCP guidelines are met”;^[17]

Thus, there is a legal requirement that COI be identified and managed; it is therefore strange that some authors believe that there is no legal requirement for declaration of COI.^[18]

In 2009, the World Medical Association in its 60th general assembly in Delhi adopted the “WMA Statement on Conflict of Interest”.^[19] It emphasized the need to disclose and manage COI both in clinical practice and research stating,

“....All relevant and material physician-researcher relationships and interests must be disclosed to potential research participants, research ethics boards, appropriate regulatory oversight bodies, medical journals, conference participants and the medical centre where the research is conducted”.

A detailed investigation covering four clinical trials (all sponsored by multinational companies) observed that investigators were paid (significant amounts) for recruiting patients from their own practice as trial subjects. Such a practice also constitutes a COI.^[20] In addition to the principal investigator (PI) those sub-investigators who are responsible for critical functions such as screening and randomization should also be assessed for COI.

Most clinical trials are now blinded, and the investigators would find it difficult to manipulate results even if they wanted. Such a manipulation would, however, be possible at the level of the data analysis. Data management staff often decides on the statistical tests to be used, and unblinding, they could knowingly or otherwise alter data to suit the sponsors or other parties. It is extremely essential to check COI at this level, as most investigators would not even know if results were altered during analysis of data. A number of universities including that of Alaska and Columbia require examination of COI of data management personnel.

The way journals ask about and report COI of authors varies widely, leading to confusion among authors and readers. The International Committee of Medical Journal Editors (ICMJE) developed an electronic COI disclosure form for usage. The form was thrown open to the public for comment and based on the feedback, a number of changes have been instituted. The major change is removal of competing interests of the author's spouse or minor children and nonfinancial competing interests.^[21]

The National Institutes of Health made significant changes in their COI policies in 2010. An important one was to lower the threshold of financial interest from \$10,000 to \$ 5000 annually. Changes in scope and disclosure were

made, but they relate to investigators receiving grants from the National Institutes of Health (NIH) only.^[22]

An EC member has brought to the notice of the author another form of COI at this level. This COI comes into play when a sponsor pays unreasonably high amounts per patient, for positive results. It is clarified that the author has no personal knowledge of any such case, yet its possibility cannot be discounted.

EC MEMBERS COI

In addition to investigators, EC members need to declare COI, as they have significant powers over the trial process. Yet, it should be realized that the EC is a multimember body and COI of one or two members may not be damaging. However, the possibility that the member with COI has a major role to play in the decision process exists. Hence, the COI of all EC members should be assessed and minimized. A study of EC member's relationships with the industry revealed that 36% members had a relationship with the industry within the past 12 months.^[23]

The Indian GCP guidelines also require the members of the EC who have a COI to declare the same and withdraw from the decision making process and the same should be recorded in the minutes (2.4.2.6.2). However, the Indian guidelines do not define the level at which investment or financial interest in a company constitutes a COI. There is an urgent need to do so.

During an EC meeting, it is recommended that any member with a COI declares the same at the beginning of the meeting and walks out when the particular project is being discussed. A declaration at the beginning of the year is practiced by some ECs; however, it does not cover changes in investments or relationships that take place continually.

Lastly, there is a negative sort of COI. A negative COI is one that occurs when loyalty toward one sponsor leads to wilful damage to a competitor's study or molecule. Such conflicts lead to an injustice to a molecule that may get eliminated from pipeline without a fair trial. Although we lay more emphasis on positive COI, it is necessary to keep the negative COI in mind too.

CONCLUSIONS

COI is a fact of life; it is going to exist and we cannot wish it away. Stake holders will have to live with multiple conflicts of interest that affect investigators, EC members, and data managers. All these COI have a potential to affect the conduct and oversight of clinical research. If we can identify and assess COIs for their potential risk and

manage them so as to minimize their impact, the integrity of research can be maintained. As a result, we can ensure that an inferior drug does not get through the process and no good drug gets rejected.

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